



Using measured logP and measured solubility to predict a compound's biopharmaceutics class

Karl Box¹, Jon Mole², Tom Gravestock¹, John Comer¹, Ruth Allen¹

¹ Sirius Analytical Ltd, Forest Row, East Sussex, UK ² Sirius Analytical Inc, Lakewood, NJ, USA

Abstract

Purpose: A method was sought for classifying which of the four classes of the Biopharmaceutics Classification Scheme (BCS) that a molecule might belong to, by accurately measuring its logP (octanol/water) and intrinsic solubility S_w , and plotting its position on a graph of logP vs. log S_w .

Methods: The logP(octanol-water) for 84 ionizable compounds, mostly drugs was measured using the potentiometric technique of dual-phase titration. The intrinsic solubility of the same set of drugs was measured using the Sirius CheqSol technique [1,2]. The literature was searched to obtain their pharmacokinetic properties, including BCS category, melting point, and information (where published) about their routes for absorption through membranes. LogP was plotted vs. log S_w in a 2-D graph, on which each point was color-coded to indicate the pharmacokinetic properties.

Results: The plot shows a number of interesting correlations. Drugs in each BCS class clustered in different parts of the graph, and while there was some overlap, the likely class could be identified with reasonable certainty. Moreover the chances of moving a molecule from one class to another could be ascertained from their position in the graph. Other clusters showed drugs which are absorbed by active transport, drugs with low melting points, and drugs with CNS activity. Because of the uncertainty in prediction, it was impossible to draw such convincing conclusions from a plot for the same drugs but made using predicted values for logP and log S_w , this underlies the case for making accurate measurements of physicochemical parameters.

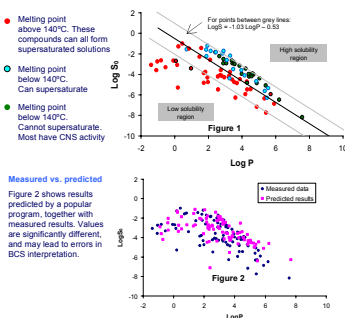
Conclusion: Measured logP plotted vs. measured intrinsic solubility is a useful indicator of a drug's BCS class.

Experimental

Measurements were made using a Sirius GLpKa titrator with D-PAS spectrometer. Measurements were performed in 0.15M KCl solution at a temperature of 25°C. The software was RefinementPro 2 and CheqSol. The acid and base titrants were 0.5M HCl and 0.5M KOH, delivered to the titration vessel through narrow bore capillaries by precision dispensers capable of delivering reproducible aliquots of known liquid volume. Deionised water of resistivity > 10¹⁴ Ω cm was used to prepare all the solutions.

Results and discussion

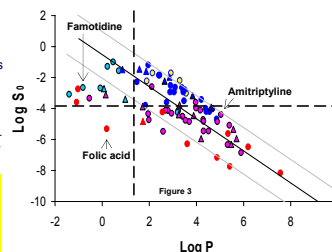
Figure 1 displays log S_w versus logP (i.e., solubility versus lipophilicity for the neutral form of the compounds). The black line gives the best fit for compounds within the grey lines which are within a range of ±1.5 logS units. Only two compounds are in the high solubility region, while many more compounds are in the low solubility region. The compounds are ranked according to melting point. The green and blue circles show compounds with melting points below 140°C while the red circles show compounds with melting points above 140°C. Note that the two compounds in the high solubility region have very low MPI below 100°C. On the low solubility side there are many compounds with MPI above 200°C. Melting points are solid state properties which show how much energy is required to break up the crystal lattice. Hence, high melting points often correlate with low solubility compounds.



Biopharmaceutics Classification System (BCS)

BCS combines information about intrinsic solubility, permeability and administered dose of a compound. A drug is considered to be highly permeable if the fraction absorbed in humans is >90%, and highly soluble if the administered dose is soluble between pH 1-8 in a volume of 250mL (the pH range of the GI tract and the volume of the luminal contents). Permeability has been shown to correlate with lipophilicity for passively transported drugs [3-4].

Figure 3 shows the 84 study compounds classified according to the BCS scheme. The BCS information was taken from information published by at least three different groups and the majority viewpoint was used. Only five compounds (marked in yellow) couldn't be classified as oral absorption data was unavailable – three of these compounds were topical anaesthetics.



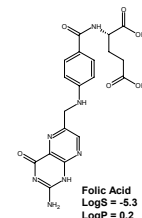
BCS Scheme More permeable (i.e. higher logP)

BCS Class	Description
III	Class III compounds are poorly absorbed but have good solubility. Permeability across intestinal membranes is rate determining. Extensions for bioequivalents have been discussed for this class. Increasing the dose may drive transport without introducing solubility problems. Class III compounds group in the top left hand corner with one exception (a potent thyroid hormone that counts as soluble because it is administered at very low doses). Membrane penetration is rate limiting because lipophilicity is too low to drive absorption.
I	Class I compounds are highly soluble and highly permeable. They are grouped in the top right hand corner. Solubility values are directly plotted on the y-axis (albeit a dosage term is incorporated in the BCS). However, lipophilicity values also seem to provide a good surrogate for oral absorption. Provided compounds are soluble and moderately lipophilic then they are also well absorbed.
IV	Class IV compounds are poorly soluble and poorly absorbed by passive transport. Those shown here have made it to the market, presumably because they are very potent, not administered by the GI route or absorbed by active transport. Interestingly, there are not many in the bottom left hand corner. Instead, there is a band of red compounds across the low solubility side, some with high lipophilicity values. The fashion of looking for highly potent and active compounds has led to large molecules with poor solubility and high lipophilicity, but they are not well absorbed.
II	Class II compounds have good absorption but solubility limits the rate of transport. They are mostly grouped in the bottom right hand corner. These compounds are sufficiently lipophilic that they are well absorbed. However, their solubility is low and rate limiting. There is no barrier to membrane penetration for the fraction of material that can dissolve.

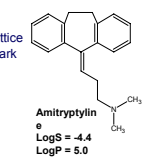
All the compounds have human fraction absorbed values greater than 20% (apart from sulfasalazine, 13%FA). Thus even the Class IV compounds in the study are well enough absorbed that they have some therapeutic benefit. But what is the driving force for membrane penetration for the compounds that are not lipophilic? In fact, many of the compounds with low logP values have active transport mechanisms (such as the vitamin folic acid) or paracellular transport has been proposed (e.g., famotidine).

Case studies

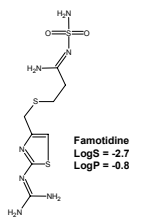
Folic acid (Vitamin M) has many H-bond donors and acceptors which contribute to a strong lattice and high melting point (250°C). These properties influence the solubility, as the breaking apart of the crystal lattice is a prerequisite of the compound dissolving. Consequently there are over five orders of magnitude difference between the solubility (LogS = -5.3) and lipophilicity (LogP = 0.2), and folic acid shows the biggest deviation from the general trend line in Figure 3. Compounds with low lipophilicity may not have sufficient driving force for membrane penetration and absorption. Nevertheless, as with many vitamins, this compound is well absorbed in the small intestine. The reason is that folic acid is actively transported across cells by receptor mediated endocytosis.



Most compounds on the high solubility side of the graph have lower melting points and weaker lattice energies. It has been shown that some of these compounds with better than average solubility (dark green in figure 1) do not form supersaturated solutions, but fall from solution as soon as their solubility limit is exceeded. However, they are nearly all well absorbed (BCS Class I or II). High permeability drives the solubilised fraction across the intestinal walls. These (dark green) compounds contain very few H-bond donating groups. Many have the ability also to cross the blood-brain barrier and therefore show CNS activity. Amitriptyline (logS = -4.4, logP = 5.0) is one such example.



Famotidine is an oral and parenteral histamine type 2-receptor antagonist, used in the treatment of gastrointestinal disorders. It competitively inhibits the binding of histamine to H2-receptors on the gastric basolateral membrane of parietal cells, reducing basal and nocturnal gastric acid secretions. Famotidine is administered orally and parenterally. The onset of action is usually within 1 hour after oral administration with maximum effects occurring within 1-3 hours depending on the dose. It is believed to be significantly absorbed by the paracellular route, as also are furosemide and atenolol. These drugs are all of moderate MW and are relatively hydrophilic.



Conclusion

Generally, the higher the lipophilicity of a compound, the lower is its solubility. However, some compounds have much lower solubility than expected. Hydrogen bonding and high melting points contribute to poor solubility. There are very few compounds that have solubility values much higher than the inverse of their logP value. It would be interesting to find these compounds. However, are there any such compounds available within current drug classes? A significant proportion of the compounds above the trend line have few hydrogen bond donors and are known to be CNS active. Using accurately measured solubility and lipophilicity values often reveals interesting behaviour of compounds. This information could be used to guide optimisation and selection of candidate compounds. For example, within a series of compounds with similar lipophilicity it may be desirable to choose those with the best solubility for further study and optimisation. Most compounds were correctly assigned to the correct BCS category. Hence, simple physicochemical property characterization could be used to classify compounds before embarking on more complicated studies into absorption and permeability determinations.

References

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